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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
10/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,343	LIPKOWSKI ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5-9 and 11-23* is/are pending in the application.

4a) Of the above claim(s) *11-16 and 18-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5-9 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/30/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 30, 2008 has been entered.

2. New claims 17-23 have been added. Claims 2-3, 5-9, 11-16 and 17-23 are pending in this application. Applicant elected with traverse Group I (claims 2-3, 5-9 and now claim 17) and elected species (Tyr-D-Met-Gly-Phe-NH-)$_2$ on April 9, 2007. Applicant's arguments were not found persuasive and the restriction requirement was deemed proper and made FINAL in the previous office action mailed on June 26, 2007, and maintained throughout the prosecution. Claims 11-16 remain withdrawn from further consideration as being drawn to nonelected invention, and claims 18-23 are withdrawn from further consideration as being drawn to nonelected species. Claims 2-3, 5-9 and 17 are examined on the merits in this office action.

Withdrawn Objections

3. Objection to the Abstract is hereby withdrawn in view of Applicant's amendment to the Abstract.

4. Objection to claim 2 is hereby withdrawn in view of Applicant's amendment to the claim.

Maintained Rejection

35 U.S.C. 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 2-3, 6-8 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronai et al (Biochem. Biophys. Res. Comm., 1979, 91: 1239-49) in

view of Abbruscato et al (J. Neurochem., 1997, 69: 1236-45) and Kanai et al (J. Biol. Chem., 1998, 273: 23629-32).

9. Ronai et al teach the tetrapeptide-amide analog of enkephalin H-Tyr-D-Met-Gly-Phe-NH_2 and its opioid activity in guinea pig ileum (abstract). The difference between the reference and the instant claims is that the reference does not teach the elected species (Tyr-D-Met-Gly-Phe-NH-)$_2$.

10. However, Abbruscato et al teach the compound biphalin, (Tyr-D-Ala-Gly-Phe-NH-)$_2$, an opioid peptide containing two pharmocophores linked by a hydrazine bridge. When administered intracerebroventricularly, biphalin has been shown to be more potent than morphine and capable of crossing the blood-brain barrier (see abstract). Abbruscato et al attribute this potency in part to the affinity of the large neutral amino acid carrier for biphalin (see p. 1244, first column). Kanai et al teach that the large neutral amino acid carrier has affinity for methionine (see p. 23629, second column).

11. Therefore, it would have been obvious to one of ordinary skill in the art to substitute methionine for the alanine in biphalin taught by Abbruscato et al in order to mimic the tetrapeptide taught by Ronai et al, satisfying all of the limitations of claim 2. With respect to claim3, Abbruscato et al teach biphalin in combination with pharmacologically acceptable carrier, in the form of an aqueous saline solution, and formulated for direct application to the site of analgesic activity including the CNS (see p. 1237). The skilled artisan would have been motivated to make this substitution given that the large neutral amino acid carrier has a greater affinity for methionine than alanine and that the affinity of this receptor for biphalin is responsible in part for

biphalin's potency. There would have been reasonable expectation of success given that the tetrapeptide harboring methionine instead of alanine has opioid activity. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

12. Applicant argues that "unlike prior opiate compounds, do not cause respiratory depression when administered at high doses. This characteristic of the claimed compound is of great importance in their expected uses, and, significantly was not expected (see page 5, lines 28 and 29)." Applicant further argues that "the compound as claimed possesses an unexpected property, and that the compound is not obvious over the cited combination of prior art." Applicant argues that "the cumulative effect of modifications to the prior art proposed by the Examiner to somehow arrive at the claimed invention have unpredictable effects, and were known to be unpredictable by those skilled in the art at the time." In reference to Kanai teachings, Applicant argues that "the Examiner has selected, out of multiple options, the substitution of an alanine with a methionine when (a) there are multiple amino acids besides methionine disclosed in Kanai et al. and (b) two of those recited in Kanai et al., as the Examiner acknowledged, are superior to methionine for the role that the Examiner has indicated is the reason for their substitution. Thus, the Examiner is arguing that the substitution with an inferior choice of amino acid is obvious."

13. Applicant's arguments have been fully considered but have not been found persuasive because Ronai et al teach the monomer of Tyr-D-Met-Gly-Phe-NH_2 and Abbruscato et al teach the compound biphalin (Tyr-D-Ala-Gly-Phe-NH-)$_2$ and has shown that biphalin has been shown to be more potent than morphine and capable of crossing the BBB. In regards to Applicant's arguments that "unlike prior opiate compounds, do not cause respiratory depression when administered at high doses. This characteristic of the claimed compound is of great importance in their expected uses, and, significantly was not expected", Table I discloses the 14 amino acid sequences of the peptide studied, but does not show the numbers, and the specification does not compare the results of the biphaline analogues to other opiods that are known to cause respiratory depression.

As described in the Advisory Action, since Abbruscato et al teach the dimerization of a well known pharmacophore (enkephaline) and shows the increased potency and crossing the BBB capability, it would have been obvious to one of ordinary skill in the art to combine the teachings, and make a dimer of Tyr-D-Met-Gly-Phe-NH, since Ronai et al indicate the increased in potency of this monomer.

Furthermore, Kanai et al teach that the large neutral amino acid carrier has affinity for methionine, and is limited to a number of amino acids (8 including methionine), and methionine worked as well as the other amino acids. In regards the Applicant's argument that "the Examiner has selected, out of multiple options, the substitution of an alanine with a methionine when (a) there are multiple amino acids besides methionine disclosed in Kanai et al. and (b) two of those recited in Kanai et al.,

as the Examiner acknowledged, are superior to methionine for the role that the Examiner has indicated is the reason for their substitution. Thus, the Examiner is arguing that the substitution with an inferior choice of amino acid is obvious", Kanai teaches that methionine worked as well as other amino acids, excluding Phe and Trp. Just because the other amino acids are "inferior" to Phe and Trp does not take away from trying these amino acids (5 other). Figure 2A of Kanai teaches that Met and Phe were about the same, and Trp and Val residues had higher % uptake of the L-leucine. FIgure 2B shows that Phe and Trp had better amino acid uptake than the other 6 amino acids. Figure 2C shows that Phe and Met were about the same for D-isomers of the amino acids. Therefore, any one of these amino acids can be picked and tried for Alanine substitution. Any of the 8 amino acids listed in Kanai reference could have been tried to see which one gave the best results, since Figure 2 shows differing results among the 8 amino acids. The MPEP states the following: "A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness; however, "the nature of the teaching is highly relevant and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use" (see MPEP 2145).

Furthermore, Ronai et al clearly indicate "decrease of potency in MVD but not in GPI"; "fall in potency in MVD and significant increase in GPI"; "loss of activity in MVD and to an enhancement in GPI". This indicates that the enkephalin agonists are specific towards different species. Therefore, one would be motivated to modify the C-terminus

of the peptide and make a dimeric peptide analog of enkephalin that contains two pharmacophores lined by a hydrazide bridge, since Abbruscato et al teaches that (Tyr-D-Ala-Gly-Phe-NH-)$_2$ was the most potent analgesic enkephalin analog that was studied to date. Kanai et al teach that the large neutral amino acid carrier has affinity for methionine, and since Ronai et al teaches the monomeric sequence (Tyr-D-Met-Gly-Phe-NH_2) showed significant increase in potency (alters drastically the binding properties of an enkephalin analog), and Abbruscato et al showed that dimeric peptide analog of enkephalin linked by a hydrazide bridge had the most potent activity, it would have been obvious to substitute Met for Ala, to see what effect it would have on the analog potency and transport system. The instant specification list (Tyr-D-Ala-Gly-Phe-NH-)$_2$ as one of biphaline compounds tested (see paragraph [0006] and Table I of instant specification US 2006/0241053 A1). This is the same biphaline compound cited in Abbruscato reference. Since the properties and functionality are inherent characteristics of the compound, it would have been obvious to try and produce other biphaline and biphaline analog compounds and expect at least the same or similar properties and functionalities. There is a reasonable expectation of success, since both Ronai and Abbruscato references teach enkephalin analogs that showed significant increase in potency.

Applicant has directed the Examiner to page 5, lines 28 and 29 of the instant specification. However, the lines do not recite what Applicant has indicated, i.e., "great importance in their expected uses, and, significantly was not expected." The page 5, lines 28 and 29 is a listing of biphaline analogs in Table I.

14. Claims 2-3, 5-9 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronai et al (Biochem. Biophys. Res. Comm., 1979, 91: 1239-49), Abbruscato et al (J. Neurochem., 1997, 69: 1236-45) and Kanai et al (J. Biol. Chem., 1998, 273: 23629-32) as applied to claims 2-3 and 6-8 above in further view of Hill (US Patent # 5880132), Bock et al (EP 0434369 A1) and Ornstein (US Patent # 5356902).

15. Ronai et al, Abbruscato et al and Kanai et al do not teach the administration of (Tyr-D-Met-Gly-Phe-NH-)$_2$ in combination with compounds that block stimulatory amino acid, tachykinin or cholecystokinin receptors (claim 5) or in combination with biphalin.

16. Ornstein teaches stimulatory amino acid antagonists, decahydroisoquinoline compounds, and their use as analgesic compounds (column 2, lines 6 and 7). Hill teaches pharmaceutical compositions comprising both piperidine tachykinin antagonist and opioid analgesics (abstract). Bock et al teach cholecytokinin antagonists and their ability to potentiate morphine and other analgesics.

17. Therefore, it would have been obvious to one of ordinary skill in the art to combine the (Tyr-D-Met-Gly-Phe-NH-)$_2$ analgesic taught by combination of Ronai et al, Abbruscato et al and Kanai et al and the stimulatory amino acid, tachykinin or cholecystokinin receptor antagonists taught by Ornstein, Hill and Bock et al or the biphalin taught by Abbruscato et al. The skilled artisan would have been motivated to do so given that the prior art teaches that compounds such as (Tyr-D-Met-Gly-Phe-NH-)$_2$ and biphalin have the same or complimentary functions as stimulatory amino acid, tachykinin or cholecystokinin receptor antagonists. There would have been a reasonable expectation of success given that the stimulatory amino acid, tachykinin or

cholecystokinin receptor antagonists and their pharmaceutical use are well-known in the prior art and compatible with opioid analgesics. The MPEP states in section 2144.06: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)" Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

18. Applicant argues that "Applicant has stated hereinabove why the invention as claimed is not obvious over the combination of Roani et al., Abbruscato et al., and Kanai et al. Applicant further note that the teachings of Hill et al., Bock et al. and Ornstein, in combination with the remaining cited art, do not cure these deficiencies."

19. Applicant's arguments have been fully considered but have not been found persuasive because the prior arts combined teach or suggest Applicant's invention. Response to Applicant's arguments for Ronai, Abbruscato and Kanai references are stated above. As discussed above, Ornstein teaches stimulatory amino acid antagonists, decahydroisoquinoline compounds, and their use as analgesic compounds (column 2, lines 6 and 7). Hill teaches pharmaceutical compositions comprising both piperidine tachykinin antagonist and opioid analgesics (abstract). Bock et al teach cholecytokinin antagonists and their ability to potentiate morphine and other analgesics.

Since stimulatory amino acid, tachykinin or cholecystokinin receptor antagonists and their pharmaceutical use are well-known in the prior art and compatible with opioid analgesics, there is a reasonable expectation of success and motivation to combine the teachings. Therefore, the rejection is maintained.

Conclusion

20. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. H./
Examiner, Art Unit 1654

/Anish Gupta/

Primary Examiner, Art Unit 1654